OBSTETRICS

Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study

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BACKGROUND: Antiphospholipid syndrome is an autoimmune, hypercoagulable state that is caused by antiphospholipid antibodies. Anticardiolipin antibodies, anti-β2 glycoprotein-I, and lupus anticoagulant are the main autoantibodies found in antiphospholipid syndrome. Despite the amassed body of clinical knowledge, the risk of obstetric complications that are associated with specific antibody profile has not been well-established.

OBJECTIVE: The purpose of this study was to assess the risk of obstetric complications in women with primary antiphospholipid syndrome that is associated with specific antibody profile.

STUDY DESIGN: The Pregnancy In Women With Antiphospholipid Syndrome study is a multicenter, retrospective, cohort study. Diagnosis and classification of antiphospholipid syndrome were based on the 2006 International revised criteria. All women included in the study had at least 1 clinical criteria for antiphospholipid syndrome, were positive for at least 1 antiphospholipid antibody (anticardiolipin antibodies, anti-β2 glycoprotein-I, and/or lupus anticoagulant), and were treated with low-dose aspirin and prophylactic low molecular weight heparin from the first trimester. Only singleton pregnancies with primary antiphospholipid syndrome were included. The primary outcome was *live birth*, defined as any delivery of a live infant after 22 weeks gestation. The secondary outcomes were preeclampsia with and without severe features, intrauterine growth restriction, and stillbirth. We planned to assess the outcomes that are associated with the various antibody profile (test result for lupus anticoagulant, anticardiolipin antibodies, and anti-β2 glycoprotein-I).

RESULTS: There were 750 singleton pregnancies with primary antiphospholipid syndrome in the study cohort: 54 (7.2%) were positive for lupus anticoagulant only; 458 (61.0%) were positive for anticardiolipin antibodies only; 128 (17.1%) were positive for anti-β2 glycoprotein-I only; 90 (12.0%) were double positive and lupus anticoagulant negative, and 20 (2.7%) were triple positive. The incidence of live birth in each of these categories was 79.6%, 56.3%, 47.7%, 43.3%, and 30.0%, respectively. Compared with women with only 1 antibody positive test results, women with multiple antibody positive results had a significantly lower live birth rate (40.9% vs 56.6%; adjusted odds ratio, 0.71; 95% confidence interval, 0.51—0.90). Also, they were at increased risk of preeclampsia without (54.5% vs 34.8%; adjusted odds ratio, 1.56; 95% confidence interval, 1.22—1.95) and with severe features (22.7% vs 13.8%, adjusted odds ratio, 1.66; 95% confidence interval, 1.19—2.49), of intrauterine growth restriction (53.6% vs 40.8%; adjusted odds ratio, 2.31; 95% confidence interval, 1.17—2.61) and of stillbirth (36.4% vs 21.7%; adjusted odds ratio, 2.67; 95% confidence interval, 1.22—2.94). In women with only 1 positive test result, women with anti-β2 glycoprotein-I positivity present alone had a significantly lower live birth rate (47.7% vs 56.3% vs 79.6%; $P<.01$) and a significantly higher incidence of preeclampsia without (47.7% vs 34.1% vs 11.1%; $P<.01$) and with severe features (17.2% vs 14.4% vs 0%; $P=.02$), intrauterine growth restriction (48.4% vs 40.1% vs 25.9%; $P<.01$), and stillbirth (29.7% vs 21.2% vs 7.4%; $P<.01$) compared with women with anticardiolipin antibodies and with women with lupus anticoagulant present alone, respectively. In the group of women with >1 antibody positivity, triple-positive women had a lower live birth rate (30% vs 43.3%; adjusted odds ratio,0.69; 95% confidence interval, 0.22—0.91) and a higher incidence of intrauterine growth restriction (70.0% vs 50.0%; adjusted odds ratio,2.40; 95% confidence interval, 1.15—2.99) compared with double positive and lupus anticoagulant negative women.

CONCLUSION: In singleton pregnancies with primary antiphospholipid syndrome, anticardiolipin antibody is the most common sole antiphospholipid antibody present, but anti-β2 glycoprotein-I is the one associated with the lowest live birth rate and highest incidence of preeclampsia, intrauterine growth restriction, and stillbirth, compared with the presence of anticardiolipin antibodies or lupus anticoagulant alone. Women with primary antiphospholipid syndrome have an increased risk of obstetric complications and lower live birth rate when <1 antiphospholipid antibody is present. Despite therapy with low-dose aspirin and prophylactic low molecular weight heparin, the chance of a liveborn neonate is only 30% for triple-positive women.

Key words: antiphospholipid antibody, autoimmune disorder, preeclampsia, preterm birth, thrombophilia

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Antiphospholipid syndrome (APS) is an autoimmune, hypercoagulable state caused by evidence of antiphospholipid antibodies (APA) [1] that is defined as venous or arterial thrombosis and/or pregnancy morbidity in patients with persistent laboratory evidence of APA. Anticardiolipin antibodies (aCL), anti-β2 glycoprotein-I (ab2GPI), and lupus anticoagulant (LA) are the main autoantibodies found in APS.[2]

There are 2 types of APS: primary APS refers to a patient with APS but no other autoimmune disorders; secondary APS refers to a patient with other

TABLE 1
Clinical (must meet at least 1) and laboratory (must meet at least 1) criteria for the diagnosis of antiphospholipid syndrome based on the 2006 International consensus statement[2]

Clinical criteria			
Vascular thrombosis: ≥1 clinical episodes of arterial, venous, or small vessel thrombosis	Pregnancy morbidity: ≥1 unexplained fetal death at ≥10 weeks gestation	Pregnancy morbidity: ≥1 preterm births at <34 weeks gestation because of severe preeclampsia or intrauterine growth restriction	Pregnancy morbidity: ≥3 unexplained pregnancy losses at <10 weeks gestation

Laboratory criteria[a]		
Lupus anticoagulant[b]	Anticardiolipin antibody of immunoglobulin G or M isotype >40 GPL or MPL, or >99th percentile with the use of commercially available enzyme-linked immunosorbent assay	Anti-β2 glycoprotein-I of immunoglobulin G or M isotype in titer >99th percentile for a normal population as defined by the laboratory performing the test with the use of commercially available enzyme-linked immunosorbent assay

GPL, G phospholipids; *MPL*, M phospholipids.

[a] Abnormal laboratory tests must occur on >1 occasion, ≥12 weeks apart, and within a 5-year time frame; [b] Examples are lupus anticoagulant, dilute Russell's viper venom time, or activated partial thromboplastin time test.

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autoimmune disorders that include systemic lupus erythematosus.[1,2]

Pregnant women with APS are at increased risk of obstetric complications that include pregnancy loss, preeclampsia, intrauterine growth restriction (IUGR), stillbirth, and preterm birth (PTB).[1] According to the American College of Obstetricians and Gynecologists (ACOG), in women with APS, prophylactic doses of heparin and low-dose aspirin during pregnancy should be considered.[3] However, despite the amassed body of clinical knowledge,[1-3] the risk of obstetric complications according to the APA profile has not been well-established and is still subject of debate.[1-3]

Thus, the aim of our study was to assess the risk of obstetric complications in women with primary APS according to the APA profile (test result for LA, aCL, and ab2GPI).

Methods

Study design and participants

The PREGNANTS (PREGNancy in women with ANTiphospholipid Syndrome) study is multicenter, retrospective, cohort study. Clinical records of all consecutive pregnant women with primary APS, who were referred to 7 Italian University Hospitals (University of Naples "Federico II," University of Bologna, University of Parma, University of Modena, University of Udine, University of Padua, and University of Roma "Tor Vergata") from January 2007 to April 2016, were collected in a dedicated merged database. Data for all consecutive women with singleton pregnancies who previously had had a diagnosis of primary APS[2] and were referred to our Divisions for counselling were included in the database. Only women with singleton pregnancies and only those who were visited at least once in the first trimester (<12 weeks) of their pregnancy were analyzed. Women with multiple pregnancies were excluded.

Antiphospholipid antibodies testing and management

At the first trimester visit, all women were counselled; APA was tested for confirmatory testing, and therapy was begun.

Women were tested for aCL, ab2GPI, and LA and were treated with both low-dose aspirin (100 mg per day) and prophylactic low molecular weight heparin (LMWH; dalteparin 5000 U subcutaneously every 12 hr) in case of no history of arterial or venous thrombosis.[3] In case of a history of thrombosis, women were treated with LMWH at therapeutic levels (either enoxaparin 1 mg/kg every 12 hr subcutaneously or dalteparin 200 U/kg every 12 hr subcutaneously). Therapy was begun as soon as APS was confirmed and continued until 6 weeks after delivery.[3] If venous thromboembolism (VTE) occurred during the current pregnancy, women were then treated with LMWH at therapeutic levels.[3]

Women who did not received low-dose aspirin and LMWH starting from the first trimester (<12 weeks gestation) and those who received other therapies (eg, corticosteroids, intravenous immunoglobulin) were excluded from the analysis.

APA were tested in each participating center with the use of the same cut-offs[2] and the same techniques at a core laboratory in the first trimester[4,5] to standardize the testing across all centers.

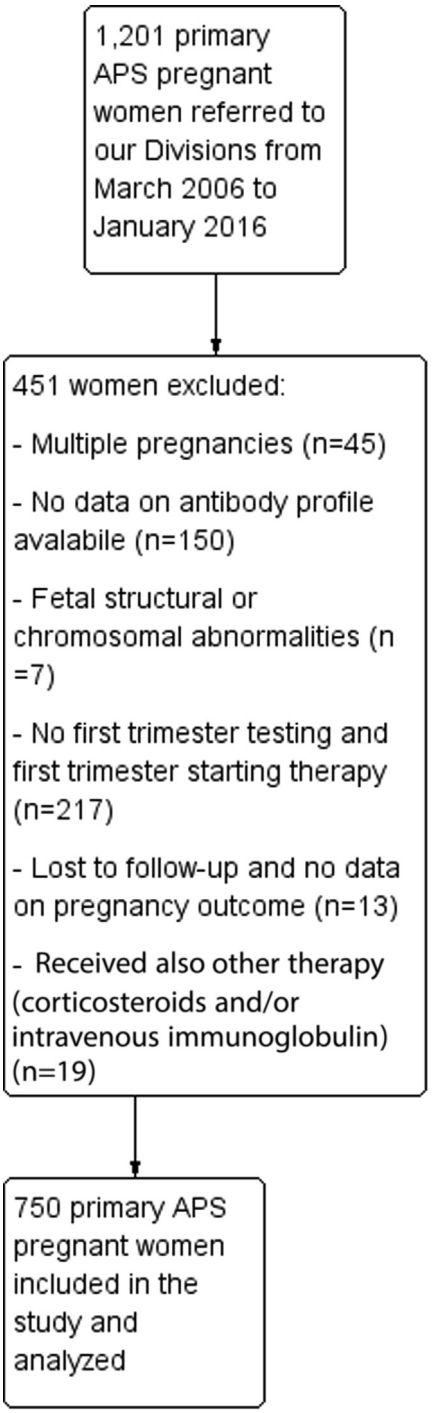
ACL

ACL was tested with the use of the standardized enzyme-linked immunosorbent assay for cardiolipin.[4]

Ab2GPI

A maxisorp microtitre plate was coated with beta 2 glycoprotein 1 antigen diluted in borate-buffered saline solution pH 9.6 and incubated at 4°C overnight. The plate was then washed 2 times

FIGURE 1
Study algorithm



Study flow chart.

APS, antiphospholipid syndrome.

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TABLE 2
Antibody profile of the 750 women included

Variable	Incidence (n=750), n (%)	Classification according to the 2006 International consensus statement[2]
LA+/aCL+/ab2GPI+	20 (2.7)	Type I (triple-positive)
LA−/aCL+/ab2GPI+	90 (12.0)	Type I (double-positive and LA negative)
LA+/aCL−/ab2GPI−	54 (7.2)	Type IIa (single-positive)
LA−/aCL+/ab2GPI−	458 (61.0)	Type IIb (single-positive)
LA−/aCL−/ab2GPI+	128 (17.1)	Type IIc (single-positive)

ab2GPI, anti-β2 glycoprotein-I; *aCL*, anticardiolipin antibody; *LA*, lupus anticoagulant.

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with borate-buffered saline solution. The plate was incubated 2 hours at room temperature. At the end of incubation, the plate was washed a further 3 times; after which, 100 μL of working strength detection antibody (goat anti-Human immunoglobulin G or M alkaline phosphatase conjugate; Sigma Chemical Company, St Louis, MO) was added to each well. Three more washes were performed. Absorbance was read on an automated microplate reader.

LA

LA was detected with the use of a panel of 3 tests that included the dilute Russell's viper venom time, a lupus anticoagulant-sensitive partial thromboplastin time, and the dilute prothrombin time.

Therefore, all women included in the study had singleton pregnancies, had a previous diagnosis of primary ASP based on the revised classification criteria (Table 1),[2] had a positive confirmatory testing in the first trimester, and received low-dose aspirin and LMWH.

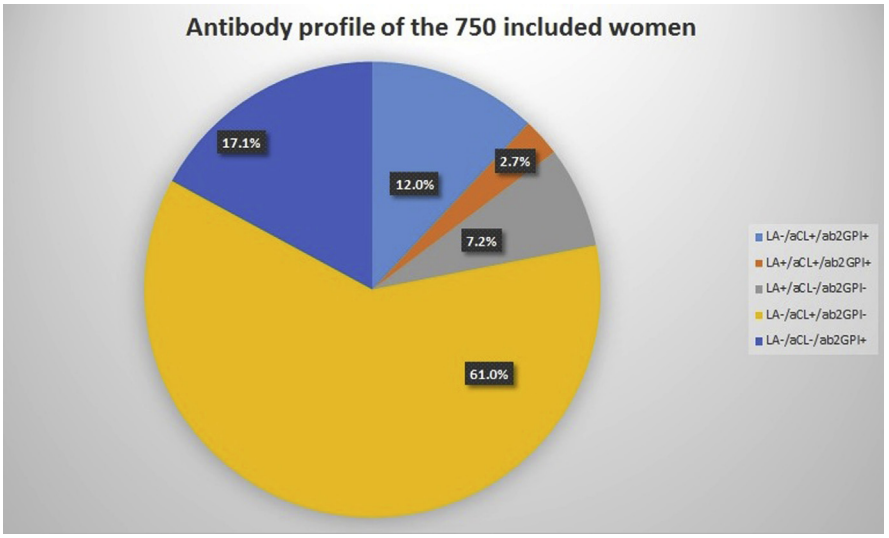
Outcomes

The primary outcome was *live birth*, defined as any delivery of a live infant at >22 weeks gestation. The main secondary outcomes were preeclampsia without severe features,[6] preeclampsia with severe features,[6] IUGR,[7] and stillbirth (fetal death at >22 weeks gestation). Other secondary outcomes were very preterm IUGR,[7] placental abruption (detachment or separation of the placenta at any time before delivery), VTE in the index pregnancy, pregnancy loss at ≤22 weeks gestation, PTB at <37 weeks gestation, and neonatal death (death of a live-born baby within the first 28 days of life). Given that women with history of VTE have worse pregnancy outcomes compared with those without a history of VTE,[1-3] we planned to assess the primary outcome (ie, live birth) in subgroup analysis according to the history of vascular thrombosis.

Diagnosis of preeclampsia without severe features and preeclampsia with severe features were based on the ACOG guidelines.[6] *IUGR* was defined as ultrasound estimated fetal weight of <10th percentile for gestational age on the reference chart.[7] Severe very preterm IUGR was considered present in women with a fetal abdominal circumference of <10th percentile for gestational age on the reference chart and abnormal umbilical artery Doppler with a pulsatility index of >95th percentile of the Doppler reference chart at 24−32 weeks.[7]

The diagnosis of APS required the presence of at least 1 clinical and 1 laboratory criteria,[4,5] as reported in Table 1.[2] Women with primary APS were divided into 2 groups according to the antibody profile[2]: type I, >1 laboratory criterion present in any combination; type II, positivity to a single test alone. The type I women were then divided into 2 subgroups: those with triple positivity and those with double positivity. The type II women were divided into 3 subgroups: IIa (LA present alone), IIb (aCL present alone), and IIc (ab2GPI present alone).[2]

FIGURE 2
Antibody profile of the 750 women who were included



Antibody profile of the 750 included women.

ab2GPI, anti-β2 glycoprotein-I; *aCL*, anticardiolipin antibody; *LA*, lupus anticoagulant.

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Positive antibodies were underlined through the text to make them easier to read.

To assess the strongest antibody prognostic marker and to assess the chance of a liveborn neonate and likelihood of obstetric complications in each antibody profile, we assessed the primary and the secondary outcomes in the following analyses, separately: type I (either LA−/aCL+/ab2GPI+ or LA+/aCL+/ab2GPI+) vs type II women (either LA+/aCL−/ab2GPI− or LA−/aCL+/ab2GPI− or LA−/aCL−/ab2GPI+); type IIa (LA+/aCL−/ab2GPI−) vs IIb (LA−/aCL+/ab2GPI−) vs IIc (LA−/aCL−/ab2GPI+); and triple-positive (LA+/aCL+/ab2GPI+) vs double-positive.

Statistical analysis

Statistical analysis was performed with the use of Statistical Package for Social Sciences software (version 19.0; IBM Inc, Armonk, NY).

Data are shown as means±standard deviation or as medians (range) or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the Fisher's exact test. Comparisons between groups were performed with the use of the Mann-Whitney *U* test to test group medians with range and with the use of the *T*-test or the 1-way analysis of

TABLE 3
Characteristics of the 110 type I (ie, >1 antibody positivity) and the 640 type II (ie, positivity to a single test alone) pregnant women with primary antiphospholipid syndrome

Characteristics	>1 Positive antibody (n=110; 14.7%)	Single positive antibody (n=640; 85.3%)	*P* value
Age, y[a]	27.4±4.5	28.2±9.3	.11
Ethnicity, n (%)			.14
White	99 (90.0)	600 (93.8)	
Non-white[b]	11 (10.0)	40 (6.2)	
Body mass index, kg/m^2[a]	25.3±12.4	25.8±11.2	.74
Smoking n (%)	9 (8.1)	59 (9.2)	.47
Diabetes mellitus (including gestational diabetes mellitus), n (%)	5 (4.5)	29 (4.5)	.93
Live birth history, n (%)	35 (31.8)	230 (35.9)	.24
≥1 Vascular thrombosis, n (%)	35 (31.8)	84 (13.1)	<.01[c]
≥1 Unexplained fetal death at ≥10 weeks gestation, n (%)	30 (27.3)	160 (25.0)	.19
≥1 Severe preeclampsia or intrauterine growth restriction at <34 weeks gestation, n (%)	50 (45.5)	290 (45.3)	.47
≥3 Unexplained pregnancy losses at <10 weeks gestation			.08
N (%)	27 (24.5)	155 (24.2)	
Median (range)	4.7 (3–11)	4.9 (3–10)	

[a] Data are presented as mean difference±standard deviation; [b] Includes Hispanic, Asiatic, Black African; [c] Statistically significant.

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TABLE 4
Primary and secondary outcomes in the 110 type I (ie, with >1 antibody positivity) and in the 640 type II (ie, positivity to a single test alone) pregnant women with primary antiphospholipid syndrome

Outcome	<1 Positive antibody (n=110; 18.3%), n (%)	Single positive antibody (n=640; 81.7%), n (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)[a]	Adjusted odds ratio (95% confidence interval)[b]
Live birth	45 (40.9)	362 (56.6)	0.70 (0.54–0.90)[c]	0.71 (0.51–0.90)[c]	0.71 (0.45–0.91)[c]
Preeclampsia without severe features	60 (54.5)	223 (34.8)	1.56 (1.27–1.93)[c]	1.56 (1.22–1.95)[c]	1.55 (1.20–1.95)[c]
Preeclampsia with severe features	25 (22.7)	88 (13.8)	1.64 (1.09–2.47)[c]	1.66 (1.19–2.49)[c]	1.66 (1.19–2.79)[c]
Intrauterine growth restriction	59 (53.6)	261 (40.8)	2.55 (1.07–2.59)[c]	2.31 (1.17–2.61)[c]	2.29 (1.07–2.65)[c]
Severe very preterm intrauterine growth restriction	31 (28.2)	86 (13.4)	2.09 (1.44–3.04)[c]	2.09 (1.34–3.24)[c]	2.09 (1.14–3.54)[c]
Placenta abruption	2 (1.8)	1 (0.2)	22.12 (1.07–457.47)[c]	20.02 (0.77–551.71)	31.02 (0.77–751.71)
Venous thromboembolism in the current pregnancy	20 (18.2)	37 (5.8)	3.69 (2.24–6.08)[c]	2.86 (2.14–7.08)[c]	2.89 (2.14–7.18)[c]
Pregnancy loss	25 (22.7)	139 (21.7)	1.04 (0.71–1.53)	1.03 (0.71–1.43)	1.03 (0.71–1.53)
Preterm birth	45 (40.9)	195 (30.5)	1.37 (1.13–1.75)[c]	1.34 (1.03–1.74)[c]	1.24 (1.03–1.84)[c]
Stillbirth	40 (36.4)	139 (21.7)	2.67 (1.24–2.88)[c]	2.67 (1.22–2.94)[c]	2.13 (1.12–2.95)[c]
Neonatal death	4 (3.6)	14 (2.2)	1.27 (0.43–3.79)	1.22 (0.44–4.12)	1.12 (0.44–4.22)

[a] Adjusted for history of vascular thrombosis (Table 3); [b] Adjusted for all variables reported in Table 3; [c] Statistically significant.
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variance to test group means with standard deviations.

Logistic regression, presented as unadjusted odds ratio (crude odds ratio) or adjusted odds ratio (aOR) with the 95% of confidence interval (CI),[8] was performed for primary and secondary outcomes. Adjusted analysis was performed to correct data for relevant baseline characteristics. Two adjusted analyses were performed, 1 in which covariates were included if they statistically differed between the antibody groups and 1 in which all potentially relevant baseline characteristics were added to the model as covariates. The latter analysis was performed to show robustness of our results.[9] All results presented in the abstract and text refer to the first adjusted analysis. A probability value of <.05 was considered to indicate statistical significance.

The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10]

Results

During the study period, there were 173,842 deliveries in the 7 centers; 1201 primary APS pregnant women (0.7%) were identified. Overall, 750 singleton pregnancies met the inclusion criteria and were analyzed retrospectively (Figure 1). Fifty-four pregnancies (7.2%) were positive for only LA; 458 pregnancies (61.0%) were positive for only aCL, and 128 pregnancies (17.1%) were positive for only ab2GPI; 90 pregnancies (12.0%) were LA−/aCL+/ab2GPI+, and 20 pregnancies (2.7%) were LA+/aCL+/ab2GPI+ (Table 2, Figure 2).

Women with only 1 antibody positive test results vs women with multiple positive results

Characteristics of the women

Women with positivity to >1 antibody test were in general comparable in terms of baseline characteristics but had a significantly higher rate of previous vascular thrombosis compared with women with positivity to a single test alone (31.8% vs 13.1%; $P<.01$; Table 3).

Primary and secondary outcomes

Compared with women with only 1 antibody positive test results, women with multiple positive results had lower live birth rates (40.9% vs 56.6%; aOR, 0.71; 95% CI, 0.51–0.90) and a higher incidence of preeclampsia without (54.5% vs 34.8%; aOR, 1.56; 95% CI, 1.22–1.95) and with severe features (22.7% vs 13.8%; aOR, 1.66; 95% CI, 1.19–2.49), IUGR (53.6% vs 40.8%; aOR, 1.30; 95% CI, 1.17–2.61), severe very preterm IUGR (28.2% vs 13.4%; aOR, 2.09; 95% CI, 1.34–3.24), VTE in the current pregnancy (18.2% vs 5.8%; aOR, 2.86; 95% CI, 2.14–7.09), PTB (40.9% vs 30.5%; aOR, 1.34; 95% CI, 1.03–1.74), and stillbirth (36.4% vs 21.7%; aOR, 2.67; 95% CI, 1.22–2.94).

TABLE 5
Characteristics of the 640 type II (ie, positivity to a single test alone) pregnant women with primary antiphospholipid syndrome

Characteristics	Lupus anticoagulant alone (n=54; 8.4%)	Anticardiolipin antibody alone (n=458; 71.6%)	Anti-β2 glycoprotein-I alone (n=128; 20.0%)	*P* value
Age, y[a]	27.4±6.3	28.4±7.7	28.2±4.9	.35
Ethnicity, n (%)				.09
White n (%)	50 (92.6)	422 (92.1)	115 (89.8)	
Non-white[b]	4 (7.4)	36 (7.8)	13 (10.2)	
Body mass index, kg/m^2[a]	26.1±11.1	25.7±6.4	25.9±8.4	.53
Smoking, n (%)	5 (9.3)	51 (11.1)	19 (14.8)	.19
Diabetes mellitus (including gestational diabetes mellitus), n (%)	3 (5.6)	19 (4.1)	6 (4.7)	.43
Live birth history, n (%)	20 (37.0)	155 (33.8)	50 (39.1)	.12
≥1 Vascular thrombosis, n (%)	7 (13.0)	61 (13.3)	17 (13.3)	.71
≥1 Unexplained fetal deaths at ≥10 weeks gestation, n (%)	15 (27.8)	113 (24.7)	32 (25.0)	.76
≥1 Severe preeclampsia or intrauterine growth restriction at <34 weeks gestation, n (%)	25 (50.0)	229 (50.0)	58 (45.3)	.12
≥3 Unexplained pregnancy losses at <10 weeks gestation				.17
N (%)	15 (27.8)	133 (29.0)	35 (27.3)	
Median (range)	3.7 (3–4)	4.7 (3–10)	5.1 (3–6)	

[a] Data are presented as mean difference±standard deviation; [b] Includes Hispanic, Asiatic, Black African.
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No differences were found in the rate of placenta abruption, pregnancy loss, and neonatal mortality (Table 4).

Women with only 1 antibody positive test results

Characteristics of the women

In the group of the 640 women with positivity to a single test alone, the LA−/aCL+/ab2GPI− women were the most frequent category (n=458/640; 71.6%); the most rare antibody profile was the LA+/aCL−/ab2GPI− profile (n=54/640; 8.4%); 128 of 640 women (20.0%) were positive to ab2GPI alone (Table 2). The 3 subgroups were similar in terms of maternal demographics and medical and obstetric history (Table 5).

Primary and secondary outcomes

Women with ab2GPI present alone had a significantly lower live birth rate (47.7% vs 56.3% vs 79.6%; *P*<.01) and a significantly higher incidence of preeclampsia without (47.7% vs 34.1% vs 11.1%; *P*<.01) and with severe features (17.2% vs 14.4% vs 0%; *P*=.02), IUGR (48.4% vs 40.1% vs 25.9%; *P*<.01), severe very preterm IUGR (19.5% vs 13.1% vs 1.9%; *P*<.01), PTB (32.8% vs 30.4% vs 25.9%; *P*=.03), and stillbirth (29.7% vs 21.2% vs 7.4%; *P*<.01) compared with women with aCL and with women with LA present alone, respectively. No differences were found in the rate of placenta abruption, VTE, pregnancy loss, and neonatal death (Table 6).

Women with multiple positive results

Characteristics of the women

The group of 110 women with >1 antibody positivity included 20 women who were positive to all 3 laboratory tests (triple positivity) and 90 patients who were positive to aCL and ab2GPI but negative to LA (double positivity); none were double positive with the other 2 possible combinations (Table 7).

Primary and secondary outcomes

We found that triple-positive women had lower live birth rates (30% vs 43.3%; aOR, 0.69; 95% CI, 0.22–0.91) and a higher incidence of IUGR (70.0% vs 50.0%; aOR, 2.40; 95% CI, 1.15–2.99), severe very preterm IUGR (35.0% vs 26.7%; aOR, 1.31; 95% CI, 1.27–2.61), and placenta abruption (10.0% vs 0%; aOR, 19.77; 95% CI, 1.02–529.77) compared with double-positive and negative LA women. No differences were found in the rate of preeclampsia without and with severe features, VTE, pregnancy loss, PTB, stillbirth, and neonatal death (Table 8).

Summary of results

Table 9 is a summary table that shows the chance of a liveborn neonate and the

TABLE 6
Primary and secondary outcomes in the 640 type II (ie, positivity to a single test alone) pregnant women with primary antiphospholipid syndrome

Outcome	Lupus anticoagulant alone (n=54; 8.4%)	Anticardiolipin antibody alone (n=458; 71.6%)	Anti-β2 glycoprotein-I alone (n=128; 20.0%)	*P* value	Lupus anticoagulant alone vs anticardiolipin antibody alone		Lupus anticoagulant alone vs anti-β2 glycoprotein-I alone		Anticardiolipin antibody alone vs anti-β2 glycoprotein-I alone	
					Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)[a]	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)[a]	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)[a]
Live birth	43 (79.6)	258 (56.3)	61 (47.7)	<.01[b]	2.55 (1.22–2.66)[b]	2.41 (1.21–2.65)[b]	2.69 (1.33–3.11)[b]	2.67 (1.33–3.10)[b]	2.21 (1.13–2.34)[b]	2.18 (1.13–2.44)[b]
Preeclampsia without severe features	6 (11.1)	156 (34.1)	61 (47.7)	<.01[b]	0.31 (0.17–0.64)[b]	0.33 (0.15–0.70)[b]	0.20 (0.11–0.41)[b]	0.23 (0.11–0.51)[b]	0.70 (0.57–0.82)[b]	0.71 (0.57–0.89)[b]
Preeclampsia with severe features	0	66 (14.4)	22 (17.2)	.02[b]	0.07 (0.04–0.74)[b]	0.06 (0.03–1.01)	0.05 (0.01–0.74)[b]	0.05 (0.01–0.84)[b]	0.82 (0.55–0.93)[b]	0.84 (0.54–0.94)[b]
Intrauterine growth restriction	14 (25.9)	185 (40.4)	62 (48.4)	<.01[b]	0.62 (0.41–0.82)	0.64 (0.40–0.89)[b]	0.50 (0.33–0.87)[b]	0.54 (0.33–0.87)[b]	0.81 (0.65–0.94)[b]	0.83 (0.68–0.95)[b]
Severe very preterm intrauterine growth restriction	1 (1.9)	60 (13.1)	25 (19.5)	<.01[b]	0.14 (0.02–0.88)[b]	0.14 (0.02–0.91)[b]	0.09 (0.03–0.71)[b]	0.09 (0.03–0.71)[b]	0.67 (0.55–0.91)[b]	0.67 (0.55–0.92)[b]
Placenta abruption	0	0	1 (0.8)	.52	Not estimable	Not estimable	0.77 (0.03–10.89)	0.78 (0.03–18.89)	0.09 (0.03–2.28)	0.09 (0.03–2.28)
Venous thromboembolism in the current pregnancy	3 (5.6)	28 (6.1)	6 (4.7)	.41	0.90 (0.29–1.99)	0.91 (0.29–2.89)	1.19 (0.31–4.03)	1.19 (0.31–4.57)	1.30 (0.55–2.73)	1.30 (0.55–3.03)
Pregnancy loss	7 (13.0)	103 (22.5)	29 (22.7)	.23	0.55 (0.28–1.01)	0.58 (0.28–1.17)	0.57 (0.27–1.22)	0.57 (0.27–1.23)	0.94 (0.58–1.30)	0.95 (0.58–1.31)
Preterm birth	14 (25.9)	139 (30.4)	42 (32.8)	.03[b]	0.83 (0.53–1.05)	0.85 (0.53–1.37)	0.74 (0.47–0.80)[b]	0.79 (0.47–0.84)[b]	0.77 (0.70–0.92)[b]	0.81 (0.70–0.92)[b]
Stillbirth	4 (7.4)	97 (21.2)	38 (29.7)	<.01[b]	0.37 (0.13–0.89)[b]	0.35 (0.13–0.91)[b]	0.25 (0.13–0.56)[b]	0.25 (0.13–0.66)[b]	0.71 (0.62–0.88)[b]	0.71 (0.52–0.89)[b]
Neonatal death	0	12 (2.6)	2 (1.6)	.51	0.53 (0.02–4.56)	0.33 (0.02–5.56)	0.47 (0.12–8.61)	0.47 (0.12–9.61)	2.44 (0.38–5.40)	1.68 (0.38–7.40)

[a] Adjusted for all variables reported in Table 5; [b] Statistically significant.

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TABLE 7
Characteristics of the 110 type I (ie, with >1 antibody positivity) pregnant women with primary antiphospholipid syndrome

Characteristic	Triple-positive (n=20; 18.2%)	Double-positive and lupus anticoagulant negative (n=90; 81.8%)	*P* value
Age, y[a]	27.6±8.1	27.2±6.5	.33
Ethnicity, n (%)			.97
White	18 (90.0)	81 (90.0)	
Non-white[b]	2 (10.0)	9 (10.0)	
Body mass index, kg/m^2[a]	25.1±6.7	25.4±11.3	.64
Smoking, n (%)	3 (15.0)	6 (6.7)	<.01
Diabetes mellitus (including gestational diabetes mellitus), n (%)	2 (10.0)	3 (3.3)	<.01
Live birth history, n (%)	7 (35.0)	28 (31.1)	.12
≥1 Vascular thrombosis, n (%)	7 (35.0)	28 (31.1)	.12
≥1 Unexplained fetal death at ≥10 weeks gestation, n (%)	6 (30.0)	24 (26.7)	.23
≥1 Severe preeclampsia or intrauterine growth restriction at <34 weeks gestation, n (%)	10 (50.0)	40 (44.4)	.47
≥3 Unexplained pregnancy losses at <10 weeks gestation			.11
N (%)	6 (30.0)	21 (23.3)	
Median (range)	4.9 (3–5)	4.5 (3–11)	

[a] Data are presented as mean difference±standard deviation; [b] Includes Hispanic, Asiatic, Black African.
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main secondary outcomes for each identified antibody profile. The overall rate of live birth in our cohort was 54.3% (407/750).

Subgroup analysis

Women without a history of VTE had a significantly higher live birth rate compared with women without VTE (56.6% [357/631] vs 42.0% [(50/119]; aOR, 1.80; 95% CI, 1.21–2.67; Table 10).

Comment

Main findings

In singleton pregnancies with primary APS, aCL is the most common sole antibody present (61%), but ab2GPI is the one associated with the lowest live birth rate and highest incidences of obstetric complications compared with aCL or LA alone. Poor pregnancy outcomes occurred more frequently in women with >1 antibody positivity. Triple-positive women had a significantly higher risk of obstetric complications compared with double-positive women. Chance of a liveborn neonate is only 30% for triple-positive women, although the rate is 80% for women with positivity to LA alone. Women without history of vascular thrombosis have a higher live birth rate compared with those with history of vascular thrombosis. The overall incidence of VTE during pregnancy in our cohort was 7.6%.

Strengths and limitations

Our study has several strengths. The number of the included women in our cohort is substantially higher than in previous studies on this topic.[1,2,11-14] This may be the largest and most comprehensive study published on the literature on women with primary APS.[11-14] All women were tested, in the first trimester of pregnancy, for confirmatory testing; the current latest accepted definitions and classification for APS and clinical and laboratory criteria were used.[2] The exclusion of multiple gestations from the analysis further provides for a more homogenous sample and is therefore another strength. Finally, the multicenter nature of this study makes our results generalizable.

The most important limitation of our study is the retrospective approach. We do acknowledge that some outcomes were underpowered; however, those are indeed uncommon outcomes (eg, placenta abruption, neonatal death) with an overall rate of <5%. All women who data were analyzed received low-dose aspirin and prophylactic LMWH starting from the first trimester[3]; other therapies were not analyzed. We did not assess in our cohort the changing levels of antibody titers during pregnancy, and we used the first-trimester titers.

TABLE 8
Primary and secondary outcomes in the 110 type I (ie, with >1 antibody positivity) pregnant women with primary antiphospholipid syndrome

Outcome	Triple-positive (n=20; 18.2%), n (%)	Double-positive and lupus anticoagulant negative (n=90; 81.8%), n (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)[a]	Adjusted odds ratio (95% confidence interval)[b]
Live birth	6 (30.0)	39 (43.3)	0.69 (0.34–0.87)[c]	0.69 (0.22–0.91)[c]	0.61 (0.12–0.92)[c]
Preeclampsia without severe features	11 (55.0)	49 (54.4)	1.01 (0.65–1.57)	1.01 (0.64–1.58)	1.01 (0.64–1.78)
Preeclampsia with severe features	5 (25.0)	20 (22.2)	1.45 (0.87–1.56)	1.13 (0.48–2.64)	1.06 (0.38–2.64)
Intrauterine growth restriction	14 (70.0)	45 (50.0)	2.57 (1.15–2.97)[c]	2.40 (1.15–2.99)[c]	2.39 (1.13–2.99)[c]
Severe very preterm intrauterine growth restriction	7 (35.0)	24 (26.7)	1.47 (1.25–2.01)[c]	1.31 (1.27–2.61)[c]	1.31 (1.17–2.51)[c]
Placenta abruption	2 (10.0)	0	21.67 (1.08–434.78)[c]	19.77 (1.02–529.77)[c]	22.77 (1.01–629.77)[c]
Venous thromboembolism in the current pregnancy	3 (15.0)	17 (18.9)	0.90 (0.35–2.35)	0.91 (0.41–2.13)	0.93 (0.41–2.03)
Pregnancy loss	5 (25.0)	20 (22.2)	1.13 (0.48–2.64)	1.11 (0.51–3.01)	1.10 (0.41–2.01)
Preterm birth	9 (45.0)	36 (40.0)	1.13 (0.65–1.94)	1.12 (0.65–1.94)	1.10 (0.65–1.99)
Stillbirth	9 (45.0)	31 (34.4)	1.31 (1.12–2.49)[c]	1.30 (0.74–2.28)	1.22 (0.74–2.38)
Neonatal death	2 (10.0)	2 (2.2)	4.50 (0.67–30.06)	4.44 (0.61–31.16)	4.67 (0.61–39.16)

[a] Adjusted for all variables reported in Table 7; [b] Adjusted for smoking and gestational diabetes mellitus; [c] Statistically significant.
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However, data from the Predictors of Pregnancy Outcomes: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus study[11] showed that APA levels decreased marginally during pregnancy and that changes were not associated with pregnancy outcome, which suggests that measurement of APA in the first trimester as confirmatory testing in a core laboratory is sufficient to assess the risk and that repeat testing through pregnancy is unnecessary.[3,11] The rate of adverse pregnancy outcome in our cohort was higher than previous studies for women with APS.[12-14,16-18] This could be related to the history of previous thrombosis because the incidence

TABLE 9
Primary and main secondary outcomes in pregnant women with primary antiphospholipid syndrome according to the antibody profile

Variable	Triple-positive (n=20; 2.7%), n (%)	Double-positive and lupus anticoagulant negative (n=90; 12.0%), n (%)	Lupus anticoagulant alone (n=54; 7.2%), n (%)	Anticardiolipin antibody alone (n=458; 61.0%), n (%)	Anti-β2 glycoprotein-I alone (n=128; 17.1%), n (%)
Live birth	6 (30.0)	39 (43.3)	43 (79.6)	258 (56.3)	61 (47.7)
Preeclampsia without severe features	11 (55.0)	49 (54.4)	6 (11.1)	156 (34.1)	61 (47.7)
Preeclampsia with severe features	5 (25.0)	20 (22.2)	0	66 (14.4)	22 (17.2)
Intrauterine growth restriction	14 (70.0)	45 (50.0)	14 (25.9)	185 (40.4)	62 (48.4)
Stillbirth	9 (45.0)	31 (34.4)	4 (7.4)	97 (21.2)	38 (29.7)

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TABLE 10
Primary outcome in sensitivity analysis according to the history of vascular thrombosis

Live birth rate in women without history of vascular thrombosis (n=631)	Lupus anticoagulant alone (n=48; 7.6%), n (%)	Anticardiolipin antibody alone (n=394; 62.4%), n (%)	Anti-β2 glycoprotein-I alone (n=114; 18.1%), n (%)	Double-positive and lupus anticoagulant negative (n=69; 10.9%), n (%)	Triple-positive (n= 6; 1.0%), n (%)	*P* value
Live birth	39 (81.3%)	226 (57.4%)	55 (48.2%)	34 (49.3%)	3 (50.0%)	<.01[a]
Live birth rate in women with history of vascular thrombosis (n=119)	**Lupus anticoagulant alone (n=6; 5.0%), n (%)**	**Anticardiolipin antibody alone (n=64; 53.8%), n (%)**	**Anti-β2 glycoprotein-I alone (n=14; 11.8%), n (%)**	**Double-positive and lupus anticoagulant negative (n=21; 17.6%), n (%)**	**Triple-positive (n=14; 11.8%), n (%)**	
Live birth	4 (66.7%)	32 (50.0%)	6 (42.9%)	5 (23.8%)	3 (21.4%)	<.01[a]

[a] Statistically significant.

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of adverse pregnancy outcome was considerably lower in the subgroup analysis of women without a history of vascular thrombosis (Table 10). Notably, in our cohort, women without a history of vascular thrombosis had a live birth rate of >50%, which is consistent with previous studies.[13,17,18] In the previous studies, the considerably lower sample size did not permit meaningful subgroup analysis in this subset of women.[12-14,16] An additional weakness of the study is the different treatments undergone by patients who had a history of VTE or not in regards to LMWH dosing for full anticoagulation. This is not a universal practice,[3] even if recommended by experts,[2,18] which limits that aspect of its external validity. Immunoglobulin G and M type antibodies were not analyzed separately. Data on inherited thrombophilia, including Factor V Leiden, were not available.

Interpretation

The diagnostic criteria for APS were first established in the 1999 at Sapporo, Japan,[12] and then revised in the *2006 Sydney International Consensus Statement on Investigational Classification Criteria for the APS* with the inclusion of the ab2GPI antibodies.[2]

Although the risk of VTE and of adverse pregnancy outcomes in women with APS is well-established,[1] the literature lacks data regarding risk stratification within this population according to the antibody profile.[3,13-16] In a large and comprehensive systematic review, Robertson et al[13] concluded that women with acquired thrombophilia, including APS, are at risk of experiencing VTE and complications in pregnancy. They found an increased risk of both maternal (VTE, preeclampsia, and autoimmune thrombocytopenia) and fetal (pregnancy loss and fetal death, IUGR, and preterm delivery) complications in women with primary and secondary APS. However, they did not report subgroup data according to the antibody profile.[13]

APA do not provide merely serum APS biomarkers but rather exert a direct pathogenic role in vascular and obstetric events.[2] In particular, ab2GPI provides, together with prothrombin, the main epitope targeted by APS.[14,15] In the 2012, Liu et al,[16] in a retrospective case-control study, found that, in pregnant women LA-negative APS, double-positivity may be a risk factor for pregnancy loss. However, this study was limited by the study design, by the limited outcomes assessed, and by the small sample size.[16] Recently, the PROMISSE study found that circulating angiogenic factors measured during early gestation had a high negative predictive value in ruling out the development of severe adverse outcomes among patients with systemic lupus erythematosus and/or APA syndrome.[11,17]

In the European Registry on Obstetric Antiphospholipid Syndrome study, a survey of 247 consecutive cases, Alijotas-Reig et al[18] found that women with obstetric APS showed differential characteristics than classic APS and that all laboratory test categories are needed to avoid false-negative diagnoses.[18] In a European multicenter retrospective study that included 196 women with primary and secondary APS, Alijotas-Reig et al[18] found that triple-positive women had a significantly higher risk of obstetric complications compared with single or double combinations.

The optimal treatment of women with primary APS has not been well-studied.[3,19-22] A metaanalysis of randomized trials suggested that prophylactic use of LMWH and low-dose aspirin may reduce pregnancy loss by 54% in women with APS but no history of VTE.[19] This combined therapy appears superior to low-dose aspirin alone or to prednisone.[3,19] For women with a history of VTE, prophylactic LMWH during pregnancy and until 6 weeks after delivery is recommended by ACOG; after delivery, this prophylaxis should be switched to therapy with coumadin, and these women should remain on lifelong anticoagulation therapy.[3] Warfarin therapy is safe in breast-feeding women.[3,23] Notably, most authorities advise therapeutic anticoagulation for women with APS and a history of

vascular thrombosis.[1,2,4,5,11] Corticosteroids and intravenous immunoglobulin have also been suggested.[19-22] A meta-analysis by Empson et al[19] that included 3 randomized trials showed no improvement in pregnancy outcomes in women who were treated with prednisone. Therefore, the efficacy of corticosteroids remains uncertain; because of the risks associated,[19] its use is not recommended.[3] Treatment with intravenous immunoglobulin has been evaluated in few studies, and the observations suggest that this therapy may improve pregnancy outcomes beyond that observed with heparin and aspirin.[20-22,24,25] However, because the efficacy has not been proved in appropriately powered randomized trials[24,25] and the drug is extremely expensive,[26,27] its use is discouraged.[3]

Conclusion

In summary, our findings provide evidence that pregnant women with primary APS have an increased risk of obstetric complications and lower live birth rates in case of >1 APA positivity. In women with positivity to a single test alone, ab2GPI is the one associated with the lowest live birth rate and highest incidences of preeclampsia, IUGR, very preterm IUGR, preterm delivery, and stillbirth compared with aCL or with LA alone. ■

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